REMARKS

Allowable Subject Matter

Applicants gratefully acknowledge the Examiner's indication that claims 10-12, 14, 16, 30-32, 34, 38, and 40 recite allowable subject matter. See pages 4-5 of the Office Action.

Amendments

Claims 1, 3, 5, 8, 10-16, 20, 23, 25, 28, 30-34, 36, and 39 are amended above to delete superfluous language, to correct obvious typographical errors, and to use claim language in accordance with conventional US practice. Also, claims 12, 13, 32 and 33 are amended to delete "such as." Claims 17 and 19 are converted into fluorescence assay method claims.

New claims 47-62 are directed to further aspects of the invention. See, e.g., the original claims and the Examples. Claim 47 is directed to the subject matter of the "such as" clause deleted from claim 13. Claim 48 is directed to subject matter stated to be optional in claim 3. Claims 49 and 50 are each individually directed to two aspects recited in claim 9. Claim 51 is directed to an option deleted from claim 10. Claims 52 and 58 are directed further aspects of the invention. See, e.g., page 6, line 11-page 7, line 3. Claim 53 is directed to the subject matter of the "such as" clause deleted from claim 33. Claim 54 is directed to subject matter stated to be optional in claim 23. Claims 55 and 56 are each individually directed to two aspects recited in claim 29. Claim 57 is directed to an option deleted from claim 30. Claims 59-62 are directed to oligonucleotide structures exemplified in the Examples.

Rejection under 35 USC 112, second paragraph

As noted above, claims 12, 13, 32 and 33 are amended to delete "such as"; and claims 17 and 19 are converted into fluorescence assay method claims which have antecedent basis for "assay." Withdrawal of the rejection is respectfully requested.

Rejection under 35 USC 102(b) in view of the Sessler et al.

In the rejection, it is asserted that since structural formula is presented in, e.g., claim 1

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any chemical compound which is a metal complex wherein "the metal complex is interpreted as a rare-earth metal complex" will anticipate the claimed invention. Based on this assertion, the Examiner argues that Sessler et al. (US 5,559,207).

Firstly, the rejection fails to establish anticipation of applicants' claimed invention because it fails to demonstrate that the prior art discloses each and every element of the claimed invention. For example, claim 1 recites that a biological molecule is covalently bonded to a labeling agent, and the labeling agent is a fluorescent conjugate comprising an oligonucleotide which is covalently bonded to a rare-earth metal cryptate. Compare also conjugate claim 20. The rejection makes no mention of a biological molecule and clearly fails to point out where Sessler et al. (US '207) disclose a biological molecule covalently bonded to labeling agent, in which the labeling agent is an oligonucleotide covalently bonded to a rare-earth metal cryptate. Thus, the anticipation rejection should be withdrawn.

In addition, while the rejection asserts that US '207 discloses a texaphyrin metal complex, the rejection fails to present any explanation as to why one of ordinary skill in the art would consider any texaphyrin metal complex, let alone the complexes disclose by US '207, to be a cryptate metal complex.

The rejection makes the unjustified assertion that US '207 discloses a metal compound which is "europium cryptate." In support of this assertion, the rejection cites column 3, lines 56-65. However, no mention of cryptate complexes or any other complexing structure is made in this portion of the disclosure. Instead, this portion of the disclosure only describes examples of the divalent and trivalent metal cations that have catalytic activity for performing ester bond hydrolysis.

The attached excerpt from IUPAC describes cryptands as being "macrobicyclic, macrotricyclic, etc., compounds generally having nitrogen atoms at the bridgehead positions." Further, the attached excerpt from IUPAC discloses that "coplanar cyclic polydentate ligands, **such as porphyrins, are not regarded as cryptands.**" (emphasis added). Further, the Merck index describes bicyclic "crown" ethers as cryptates and defines crown ether as macrocyclic compounds having $-CH_2-CH_2-O-$ as a repeating unit.

Compare also the cryptates disclosed by Gansow et al. (US 4,257,955) and Lehn et al.

(US 5,346,996) (copies enclosed).

Thus, the rejection presents no rationale as to why the texaphyrin complexes of US '207 would be considered by one of ordinary skill in the art to be cryptate complexes.

To establish anticipation, the prior art reference must teach explicitly or inherently every feature of the claimed invention. Moreover, in making an anticipation rejection, an examiner must show **where each and every feature of the claimed invention is described** in the allegedly anticipatory reference. See, e.g., *Ex parte Levy*, 17 USPQ2d 1461, 1462 (BOPA 1990) ["Moreover, it is incumbent upon the Examiner to identify wherein each and every facet of the claimed invention is disclosed in the applied reference. "]. The rejection does not satisfy this requirement and should be withdrawn.

For the reasons presented above, withdrawal of the rejection is respectfully requested.

Rejection under 35 USC 102(b) in view of the Sessler et al. and Zhao et al.

In the rejection, it is alleged that Zhao et al. (US 6,306,975) discloses a rare earth metal complex for use as a donor label. However, Zhao et al. do not disclose or suggest a process for constructing a conjugate of a biological molecule, an oligonucleotide covalently, and a rare-earth metal cryptate, covalently bonded. Nor does US '975 disclose or suggest such a conjugate or the use thereof in an assay.

For the reasons presented above, withdrawal of the rejection is respectfully requested.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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Date: March 13, 2006

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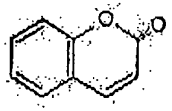
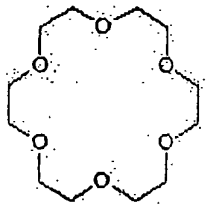
coumarins:

2*H*-Chromen-2-one (older name 1,2-benzopyrone), trivially named coumarin, and its derivatives formed by substitution. Cf. *isocoumarins*.



crown compounds:

Macrocyclic polydentate compounds, usually uncharged, in which three or more coordinating ring atoms (usually oxygen or nitrogen) are or may become suitably close for easy formation of chelate complexes with metal ions or other cationic species. (Planar analogues, such as porphyrins, are excluded.) They are also known as *coronands* and the chelate complexes are called coronates. GTPOC (crown).



E.g. a crown ether (a subclass containing only oxygen as coordinating atom.)

M. Hiraoka, *Crown Compounds: their Characteristics and Applications*, Elsevier Science Publishers, 1982.

cryptands/cryptates:

Cryptands are macrobicyclic, macrotricyclic, etc. compounds generally having nitrogen atoms at the bridgehead positions, having sufficient space within its cage structure for polydentate ligation to metal ions or other cationic species; the resulting complexes are called cryptates. E. Weber and F. Vögtle, *Inorg. Chim. Acta*, 45, L65-L67 (1980).

cycloalkanes:*

Saturated monocyclic *hydrocarbons* (with or without side chains). See alicyclic compounds. NOC Rule A-11.1. E.g. $H_2C(CH_2)_2CH_2$ cyclobutane. Unsaturated monocyclic hydrocarbons having one endocyclic double or one triple bond are called cycloalkenes and cycloalkynes, respectively. Those having more than one such multiple bond are cycloalkadienes, cycloalkatrienes, etc. The inclusive terms for any cyclic hydrocarbons having any number of such multiple bonds are cyclic *olefins* or cyclic *acetylenes*.

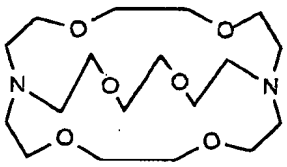
cycloalkyl groups:*

CH_2-HC–CH–

cryptand

A *molecular entity* comprising a cyclic or polycyclic assembly of *binding sites* that contains three or more binding sites held together by *covalent bonds*, and which defines a molecular cavity in such a way as to bind (and thus 'hide' in the cavity) another molecular entity, the guest (a cation, an anion or a neutral species), more strongly than do the separate parts of the assembly (at the same total concentration of binding sites). The *adduct* thus formed is called a 'cryptate'. The term is usually restricted to bicyclic or oligocyclic molecular entities.

Example:



Corresponding monocyclic ligand assemblies (*crowns*) are sometimes included in this group, if they can be considered to define a cavity in which a guest can hide. The terms 'podand' and 'spherand' are used for certain specific ligand assemblies. Coplanar cyclic polydentate ligands, such as porphyrins, are not normally regarded as cryptands.

See also *host*.

1994, *66*, 1102; 1995, *67*, 1329

Light straw-colored liq. $bp_{0.03}$ 135°. n_D^{25} 1.4988. d^{25} 1.19. Vapor pressure at 20°: 1.4 × 10^{-5} mm Hg. Soly in water at room temp: 0.1%. Slightly sol in kerosine, saturated hydrocarbons. Sol in acetone, chloroform, ethanol, highly chlorinated hydrocarbons. LD_{50} in female, male rats (mg/kg): 74, 110 orally (Gaines).

Caution: A cholinesterase inhibitor.

USE: Insecticide for external use on livestock.

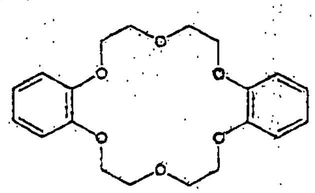
2629. Crotyl Alcohol. [6117-91-5] 2-Buten-1-ol; crotonyl alcohol. C_4H_8O; mol wt 72.11. C 66.62%, H 11.18%, O 22.19%. $CH_3CH{=}CHCH_2OH$. Prepn by reduction of crotonaldehyde: Nystrom, Brown, *J. Am. Chem. Soc.* **69**, 1197 (1947); Olivier, Young, *ibid.* **81**, 5811 (1959); Smith, Holm, US 2761883; Finch, Furman, US 2763696 (both 1956 to Shell); Foreman, US 3109865 (1963 to Standard Oil Co., Ohio). Prepn of *cis*- and *trans*-forms: Hatch, Nesbitt, *J. Am. Chem. Soc.* **72**, 727 (1950); Hickey *et al.*, *J. Org. Chem.* **21**, 429 (1956); of *cis*-form only: Clarke, Crombie, *Chem. & Ind. (London)* **1957**, 143. Toxicity study: H. F. Smyth *et al.*, *Am. Ind. Hyg. Assoc. J.* **23**, 95 (1962).

Liquid, bp 122°. d_4^{20} 0.8532. n_D^{20} 1.4285. Sol in 6 parts water; misc with alc. LD_{50} orally in rats: 0.93 ml/kg (Smyth).

cis-Form. Liquid, bp 123.6°. mp −90.15°. d_4^{20} 0.8662. n_D^{20} 1.4342.

trans-Form. Liquid, bp 121.2°. d_4^{21} 0.8454. n_D^{20} 1.4289. n_D^{25} 1.4270.

2630. Crown Ethers. Crown compounds. Macrocyclic polyethers with the repeating unit $(-CH_2-CH_2-O-)_n$ where *n* is greater than 2. Crown compounds with other heteroatoms (N, S, P) are known. Prepd by C. J. Pedersen, *J. Am. Chem. Soc.* **89**, 2495, 7017 (1967). Described as "crown" ethers due to appearance of space-filling models and ability to "crown" cations. Proposed nomenclature lists non-ring substituents, number of atoms in ring, the class (crown), and the number of heteroatoms in the ring; e.g. dibenzo-18-crown-6. Bicyclic crowns are called *cryptates*. Crowns complex with cations and solubilize inorganic reagents in organic solvents. Selectivity results from the definite size of the crown cavity which admits only cations of corresponding ionic radii. The stability of complexes depends on the size of the cation and the size of the polyether ring. Chiral crowns are used in optical resolution of enantiomers. *Reviews:* D. J. Cram, J. M. Cram, *Science* **183**, 803-809 (1974); *eidem*, *Accounts Chem. Res.* **11**, 8-14 (1978); J. J. Christensen *et al.*, *Chem. Rev.* **74**, 351-384 (1974); G. W. Gokel, H. D. Durst, *Synthesis* **1976**, 168-184; A. C. Knipe, *J. Chem. Ed.* **53**, 618-622 (1976); V. Prelog, *Pure Appl. Chem.* **50**, 893-904 (1978). Historical overview: C. J. Pedersen, *Science* **241**, 536-540 (1988).



Dibenzo-18-crown-6

18-Crown-6. 1,4,7,10,13,16-Hexaoxacyclooctadecane. $C_{12}H_{24}O_6$; mol wt 264.31. Prepn: G. W. Gokel *et al.*, *Org. Syn.* **57**, 30 (1977). Crystals from acetonitrile, mp 38-39.5°.

Dibenzo-18-crown-6. 2,3,11,12-Dibenzo-1,4,7,10,13,16-hexaoxacyclooctadeca-2,11-diene. $C_{20}H_{24}O_6$; mol wt 360.40. The first crown ether discovered. Prepn: C. J. Pedersen, US 3687978 (1972 to Du Pont). White crystals from acetone, mp 164°, bp_{670} 380-384°.

Dicyclohexano-18-crown-6. Dicyclohexyl-18-crown-6. $C_{20}H_{36}O_6$; mol wt 372.49. Approx LD in rats (mg/kg): 300 orally (Pedersen, 1967).

Caution: Direct contact may cause eye and skin irritation (Pedersen, 1967).

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